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Continuous *Versus* Intermittent Portal Triad Clamping for Liver Resection

A Controlled Study

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Objective

The authors compared the intra- and postoperative course of patients undergoing liver resections under continuous pedicular clamping (CPC) or intermittent pedicular clamping (IPC).

Summary Background Data

Reduced blood loss during liver resection is achieved by pedicular clamping. There is controversy about the benefits of IPC over CPC in humans in terms of hepatocellular injury and blood loss control in normal and abnormal liver parenchyma.

Methods

Eighty-six patients undergoing liver resections were included in a prospective randomized study comparing the intra- and postoperative course under CPC (n = 42) or IPC (n = 44) with periods of 15 minutes of clamping and 5 minutes of unclamping. The data were further analyzed according to the presence (steatosis >20% and chronic liver disease) or absence of abnormal liver parenchyma.

Results

The two groups of patients were similar in terms of age, sex, nature of the liver tumors, results of preoperative assessment, proportion of patients undergoing major or minor hepatectomy, and nature of nontumorous liver parenchyma. Intraoperative blood loss during liver transsection was significantly higher in the IPC group. In the CPC group, postoperative liver enzymes and serum bilirubin levels were significantly higher in the subgroup of patients with abnormal liver parenchyma. Major postoperative deterioration of liver function occurred in four patients with abnormal liver parenchyma, with two postoperative deaths. All of them were in the CPC group.

Conclusions

This clinical controlled study clearly demonstrated the better parenchymal tolerance to IPC over CPC, especially in patients with abnormal liver parenchyma.

The prime concern in liver surgery is to minimize blood loss and avoid transfusions, which have been shown to have a deleterious impact on both short- and long-term outcome.[1,2] This goal can be achieved by intraoperative clamping of the hepatic pedicle (inflow occlusion) or by total vascular occlusion (simultaneous inflow and outflow occlusion).[3–5] Total vascular occlusion is the safest option in patients with significant tumoral involvement of the major hepatic veins or of the inferior vena cava.[4] However, for the vast majority of liver resections that do not fall into that category, we and others have recently demonstrated that simple inflow occlusion (the Pringle maneuver) was the procedure of choice because it was associated with the least hemodynamic consequences and side effects.[3,6]

The common drawback of clamping methods is ischemic injury to the liver parenchyma. This is particularly true when there is underlying acute or chronic liver disease, making the liver very sensitive to hypoxia.[7,8] Intermittent inflow occlusion followed by short periods of reperfusion has been introduced into clinical practice and is being increasingly used.[7,9] Reperfusion after ischemia is, however, known to injure parenchymal liver cells.[10,11] Repeated episodes of ischemia–reperfusion might, therefore, be more detrimental than a single clamping session. In addition, restoration of blood flow may increase intraoperative blood loss.

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To address these issues, we have designed a prospective controlled trial comparing continuous and intermittent clamping in unselected patients undergoing liver resection, with particular attention to intraoperative blood loss, hepatocellular injury, and postoperative complications.

PATIENTS AND METHODS

Between February 1995 and March 1996, 112 patients underwent liver resection at our institution. Of these, 86 (77%) were enrolled in this study because they fulfilled the following three inclusion criteria: elective resections; total vascular exclusion not required because of involvement of the cavosuprahepatic junction or the inferior vena cava; no simultaneous bilioenteric anastomosis or associated gastrointestinal procedures.

There were 45 men and 41 women with a mean (± standard deviation) age of 51 ± 13 years (range 26–75). Indications for liver resection were mainly malignant tumors in 58 (67%) (34 hepatocellular carcinomas, 18 secondary malignancies, 5 cholangiocarcinomas, 1 gallbladder carcinoma) and benign disease in 28 (33%) (12 adenomas, 3 focal nodular hyperplasia, 3 hydatid cysts, 3 polycystic liver disease, 2 intrahepatic stones, 5 miscellaneous). Liver resection was classified into major (n = 39) and minor (n = 47) hepatectomies. Major hepatectomy procedures, defined as resection of more than three segments according to the Couinaud classification, included 17 right hepatectomies (segments 5, 6, 7, 8), 6 right lobectomies (segments 4, 5, 6, 7, 8), 7 left hepatectomies (segments 2, 3, 4), 5 extended left hepatectomies (segments 2, 3, 4, 5, 8) and 4 central hepatectomies (segments 4, 5, 8).

Intraoperative monitoring was performed by means of a pulmonary artery catheter and a radial arterial line. Central venous pressure was maintained <5 cm H_2O using early intraoperative fluid restriction. All patients were operated through an abdominal incision without opening the diaphragm and underwent intraoperative ultrasound to determine the location of the tumors and their relation to vascular branches. After abdominal exploration had ruled out extrahepatic spread, patients were randomly allocated to either continuous (CPC group) or intermittent (IPC group) clamping of the hepatic pedicle. Both clamping methods were initiated at the beginning of parenchymal transsection using a Satinsky clamp or a tourniquet. Continuous clamping was maintained until completion of the transsection. Intermittent clamping consisted of alternating sessions of clamping (15 minutes) and unclamping (5 minutes), repeated until the end of the hepatectomy. The duration of clamping and unclamping was recorded by the operating room nurses using a stopwatch ringing at 5-minute intervals. When a left hepatic artery was present, it was simultaneously occluded continuously or intermittently according to the randomization.

Parenchymal transsection was performed using an ultrasonic dissector. Hemostasis and biliostasis were obtained with bipolar electrocautery, except for large structures, which were ligated on the side of the nonresected segments and either clipped or left open on the side of the specimen. In the IPC group, transsection was stopped during the periods of unclamping and both cut surfaces were gently apposed to achieve temporary hemostasis. The tumor-free margins were checked repeatedly using intraoperative ultrasonography. Major hepatic veins that had not been extrahepatically controlled were suture-ligated as encountered. The liver cut surface at the end of the procedure was sealed with fibrin glue (LFB Laboratories, Les Ulis, France).

The amount of blood loss was measured from the weight of the soaked gauze and the volume of blood collected in the containers of the suction apparatus and the ultrasonic dissector. Because significant blood loss may occur during liver mobilization, these measurements were performed before, during, and after liver transsection. Indications for intraoperative blood transfusion were a decrease in hematocrit to 0.29 in patients with a history of cardiac disease or hemodynamic instability and to 0.24 otherwise.

Postoperative parameters of hepatocyte damage and recovery, including serum transaminase and bilirubin levels and prothrombin time (expressed as a percentage of controls), were measured on postoperative days 1, 2, 5, and 7. Abdominal ultrasound was routinely performed between postoperative days 4 and 6, as well as when an infected collection was suspected. All abdominal fluid collections were drained percutaneously and sent for bacteriologic cultures.

Liver biopsies sampled distant to the tumor were retrospectively reviewed by one senior pathologist for the presence of an underlying liver disease. These were stratified as normal (group 1, n = 50), steatotic (>20% steatosis, group 2, n = 11), or chronic liver disease (bridging fibrosis or cirrhosis, group 3, n = 25). Most patients in group 2 (9/11) had been operated on for colorectal liver metastasis. All patients in group 3 were Child's grade A, and all but one had been operated on for a hepatocellular carcinoma.

Comparison between groups were performed using the chi square test or the Fisher's exact test for qualitative variables and the Student's t test for quantitative variables. The protocol was approved by the Ethics and Research Committee of our institution.

RESULTS

After randomization (Table 1), patients were equally divided into the CPC group (n = 42) and the IPC group (n = 44). There were no significant differences between the two groups in terms of age or gender, presence of an underlying liver disease, preoperative liver function tests, indication for resection, or extent of liver resection (45% of major hepatectomies). The mean duration of pedicular clamping was also comparable, although the maximal duration was greater in the IPC group (118 *vs.* 67 minutes).

The amount of blood loss during liver transsection was significantly greater in the IPC group (Table 2). However,

Table 1. CHARACTERISTICS OF PATIENTS UNDERGOING RESECTION WITH CONTINUOUS PEDICULAR CLAMPING (CPC) AND INTERMITTENT PEDICULAR CLAMPING (IPC)

	CPC (n = 42)	IPC (n = 44)
Demographics		
Age (years) (mean ± SD)	51 ± 14	52 ± 12
Sex (M/F)	22/20	25/19
Preoperative lab tests		
Hemoglobin (g/l)	12.1 ± 2.1	12.7 ± 2.0
Prothrombin time (%)	89 ± 12	90 ± 12
Serum aspartate aminotransferase (U/l)	39 ± 29	31 ± 22
Serum alanine aminotransferase (U/l)	47 ± 45	40 ± 41
Serum bilirubin (μmol/l)	12 ± 6	12 ± 9
Indications of resection		
Benign lesions (n)	14	14
Malignant lesions (n)	28	30
Histology of nontumorous liver		
Normal liver (n)	23	27
Steatosis ≥ 20% (n)	6	5
Chronic liver disease (n)	13	12
Intraoperative characteristics		
Major hepatectomy	20	19
Ischemic duration (min)	41 ± 13	46 ± 18
Range (min)	16–67	20–118

Table 3. INFLUENCE OF CONTINUOUS PEDICULAR CLAMPING (CPC) AND INTERMITTENT PEDICULAR CLAMPING (IPC) ON POSTOPERATIVE LIVER TESTS

	CPC (n = 42)	IPC (n = 44)
Prothrombin time (%)		
Day 1	57 ± 13	59 ± 15
Day 2	60 ± 16	59 ± 16
Day 5	77 ± 16	77 ± 16
Day 7	76 ± 17	76 ± 14
Serum aspartate aminotransferase (U/l)		
Day 1	294 ± 221	264 ± 191
Day 2	301 ± 436	167 ± 133
Day 5	70 ± 59	62 ± 35
Day 7	47 ± 23	44 ± 24
Serum alanine aminotransferase (U/l)		
Day 1	358 ± 309	321 ± 247
Day 2	387 ± 363	289 ± 288
Day 5	157 ± 164	141 ± 107
Day 7	106 ± 97	102 ± 71
Serum bilirubin (μmol/l)		
Day 1	29 ± 22	28 ± 20
Day 2	28 ± 22	26 ± 21
Day 5	35 ± 42	25 ± 22
Day 7	32 ± 38	26 ± 35

the overall amount of intraoperative blood loss was not significantly different. The proportion of patients requiring an intraoperative blood transfusion (30% overall) and the number of packed red blood cells transfused were also comparable in the two groups.

Liver function tests on postoperative days 1, 2, 5, and 7 are summarized in Table 3. There was a trend toward increased cytolysis on postoperative day 2 and increased bilirubin on postoperative days 5 and 7 in the CPC group, but the difference did not reach statistical significance. Figure 1 shows the correlation between the alanine aminotransferase levels at day 2 and the duration of clamping. The correlation between alanine aminotransferase levels and duration of clamping was higher in the CPC group ($r = 0.63$, $p < 0.0001$) than in the IPC group ($r = 0.38$, $p < 0.01$). In addition, the slope of the correlation was greater in the CPC group.

The incidence of postoperative complications (Table 4) was comparable in the two groups (overall 31% *vs.* 26%, NS), except for postoperative liver failure, which developed in four patients in the CPC group and zero in the IPC group ($p = 0.05$). In all of those four patients, nontumorous liver parenchyma was abnormal, including chronic liver disease in three and 40% liver steatosis in the fourth. The two postoperative deaths occurred in patients operated on for

Table 2. INTRAOPERATIVE BLOOD LOSS AND TRANSFUSION REQUIREMENTS IN PATIENTS UNDERGOING LIVER RESECTION WITH CONTINUOUS PEDICULAR CLAMPING (CPC) OR INTERMITTENT PEDICULAR CLAMPING (IPC)

	CPC (n = 42)	IPC (n = 44)	P value
Intraoperative blood loss			
Overall (l)	1.18 ± 0.8	1.29 ± 0.9	0.42
During liver mobilization (l)	0.89 ± 0.4	0.76 ± 0.5	0.14
During liver transsection (l)	0.28 ± 0.23	0.53 ± 0.40	0.001
After liver transsection (l)	0.42 ± 0.30	0.36 ± 0.45	0.45
Transfusion requirement			
Blood transfusion (packed red cell units)	3.0	2.3	0.21
Range	0–7	0–3	
Patients transfused (%)	12 (28%)	14 (32%)	

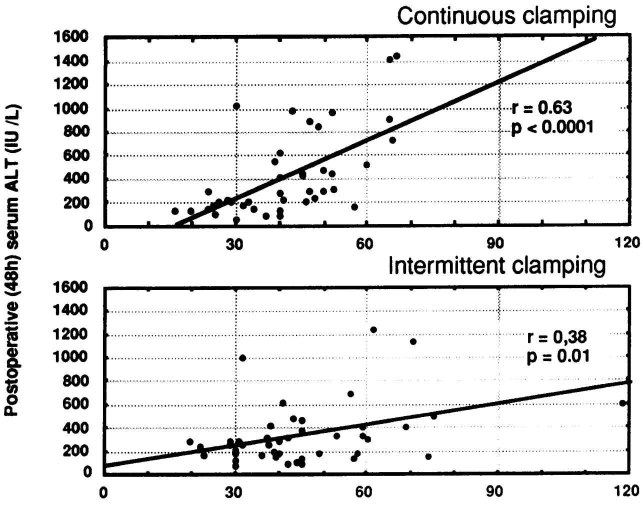

Figure 1. Correlation between duration of clamping and serum alanine aminotransferase levels on day 2 after hepatic resection with CPC and IPC.

hepatocellular carcinoma associated with chronic liver disease. One underwent a right hepatectomy with a CPC of 33 minutes and died on day 9; the other patient underwent a left lateral lobectomy with a CPC of 30 minutes and died on day 16. Of the two patients with major deterioration of liver function who survived, one, who underwent a right hepatectomy for a hydatid cyst associated with a 40% steatosis with a CPC of 65 minutes, required an emergency orthotopic liver transplant, and the other, who underwent a bisegmentectomy 5-6 for hepatocellular carcinoma associated with chronic liver disease with a CPC of 40 minutes, recovered.

Because all four patients in whom severe postoperative liver failure developed had an underlying liver disease, we next reanalyzed the postoperative kinetics of liver function tests after CPC or IPC by stratifying patients according to nontumorous liver: normal (group 1), steatotic (group 2), or chronic liver disease (group 3). Although the proportion of minor hepatectomies was greater in patients with a chronic liver disease, neither the type of clamping nor its duration was significantly different (Table 5). There was no significant difference in the duration of pedicular clamping for each group with respect to the pattern of pedicular clamping (duration of CPC *vs.* IPC): group 1, 42 ± 12 minutes *versus* 44 ± 11 minutes; group 2, 48 ± 16 minutes *versus* 49 ± 19 minutes; and group 3, 38 ± 10 minutes *versus* 47 ± 14 minutes.

The results of these analyses are summarized in Figures 2 to 4. The peak decrease in prothrombin time was significantly more important after CPC in patients with steatosis. Similarly, CPC was associated with a higher peak in serum alanine aminotransferase in patients with steatotic and chronic liver disease. Finally, CPC was associated with a greater and more prolonged increase in serum bilirubin in patients with chronic liver disease.

DISCUSSION

The aim of this study was to compare prospectively the benefits and drawbacks of CPC and IPC in unselected patients undergoing liver resection. We have shown that IPC is associated with an intraoperative blood loss comparable to that observed after CPC, but with less severe parenchymal injury, especially in patients with an underlying liver disease such as steatosis or cirrhosis.

It has now been clearly demonstrated that liver surgeons should favor reduction of blood loss and its related deaths and complications over ischemic (and/or reperfusion) injury to the liver parenchyma.[2,4,6] Although some liver resections may be performed without vascular clamping (this, for example, is a basic requirement in living-related liver transplantation), most liver resections are performed with greater safety using clamping of the hepatic pedicle.[12–14] However, with the increasing proportion of complex liver resections requiring prolonged ischemia, and patients with abnormal liver parenchyma such as steatosis and cirrhosis who are particularly sensitive to ischemia, postischemic hepatic dysfunction may occur.[8,15,16] To improve parenchymal tolerance to ischemia, IPC rather than CPC has been advocated by Far Eastern and Western investigators.[6,12,17–19] However, experimental studies have shown that cell damage after clamping is biphasic, being initiated during ischemia and then enhanced at the time of reperfusion.[20] IPC producing a series of ischemia–reperfusion injuries may therefore be expected to result in greater hepatocellular damage.[10] However, some experimental studies have shown that postoperative liver damage was less severe after IPC.[21,22] De-

Table 4. OVERALL POSTOPERATIVE COMPLICATIONS AND HOSPITAL DEATHS OF PATIENTS UNDERGOING RESECTION IN THE CONTINUOUS PEDICULAR CLAMPING GROUP (CPC) AND IN THE INTERMITTENT PEDICULAR CLAMPING (IPC) GROUP

	CPC (n = 42)	IPC (n = 44)
Complications		
Major liver deterioration	4 (2)	0
Pleural effusion	3	5
Chest infection	2	0
Subphrenic collections	3	4
Infected	2	0
Hematoma	1	1
Reoperation	2	0
Biliary fistula	1	1
Pancreatitis	0	1
In-hospital stay (days) (mean ± SD)	14 ± 8	15 ± 10
Range (days)	6–46	7–50
In-hospital death	2	0

Values in parentheses are the number of patients dying from the complication.

Table 5. CLINICAL, BIOLOGIC, HISTOLOGIC, AND INTRAOPERATIVE DATA OF PATIENTS ACCORDING TO THE NATURE OF UNDERLYING LIVER PARENCHYMA

	Group 1 (n = 50)	Group 2 (n = 11)	Group 3 (n = 25)
Age (years) (mean ± SD)	46 ± 12	58 ± 11	59 ± 11
Sex (M/F)	22/28	6/5	19/6
Prothrombin time (%)	92 ± 10	93 ± 11	82 ± 12
Serum aspartate aminotransferase (U/l)	26 ± 16	42 ± 34	51 ± 30
Serum alanine aminotransferase (U/l)	31 ± 21	71 ± 78	59 ± 32
Serum bilirubin (μmol/l)	11 ± 8	12 ± 4	16 ± 7
No. of benign/malignant lesions	24/26	1/10	1/24
Major hepatectomy	30 (60%)	4 (36%)	5 (20%)
Minor hepatectomy	20 (40%)	7 (64%)	20 (80%)
Continuous pedicular clamping (CPC)	23 (46%)	6 (54%)	13 (52%)
Intermittent pedicular clamping (IPC)	27 (54%)	5 (46%)	12 (48%)
Ischemic duration (min)	43 ± 16	49 ± 18	42 ± 13
Ischemic duration (range)	(20–118)	(20–75)	(16–74)

Group 1: patients with normal liver; group 2: patients with steatosis ≥20%; group 3: patients with chronic liver disease.

spite this, many Western surgeons are still reluctant to use IPC.[4,23] This controlled study was therefore designed to compare both methods in the clinical setting.

Our first observation was the better parenchymal tolerance to IPC. This finding is supported by a lower rise in postoperative serum transaminase levels in the IPC group despite identical overall durations of ischemia. In addition, the analysis of correlation between the duration of clamping and postoperative transaminase levels showed a higher rate of transaminase levels in the CPC group after 30 minutes of clamping. Moreover, we have found, like others, that the maximal duration of normothermic ischemia, classically set at 60 minutes, could be safety extended to 120 minutes using IPC.[18,19] Multiple short ischemia–reperfusion cycles were less deleterious than one continuous period of the same duration, suggesting that IPC can act as preconditioning.[24] The use of ischemia cycles not exceeding 15 minutes in the IPC group was based on the fact that this period was the optimal ischemic period to avoid irreversible liver cell damage, as demonstrated in experimental models.[25]

When the results of the two methods of clamping were compared in the subgroup of patients with fatty and cirrhotic livers, the superiority of IPC over CPC was even more striking. In this subgroup, serum transaminase levels were significantly higher in the CPC group. Moreover, the serum bilirubin level was significantly higher in the cirrhotic group. In addition, both fatal liver failures occurred in the patients with cirrhotic livers who had undergone CPC, although the extent of resection had been adjusted to the liver functional reserve and the duration of clamping had been <35 minutes.

The second major issue addressed by the current study is intraoperative bleeding, because a major drawback attributed to IPC is the risk of increased blood loss. Interestingly,

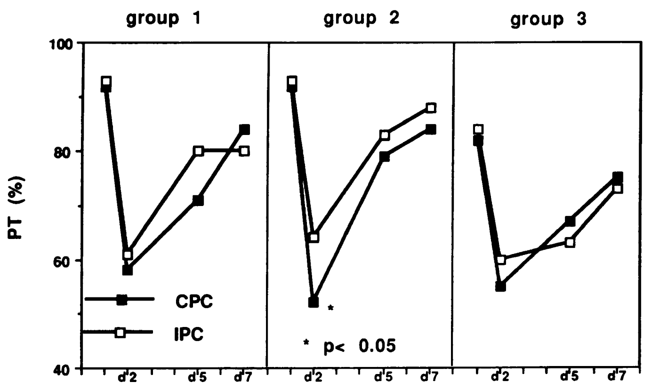

Figure 2. Serial changes in prothrombin time in patients after hepatic resection with CPC and IPC, according to the nature of underlying liver parenchyma: group 1, patients with normal liver; group 2, patients with steatosis ≥20%; and group 3, patients with chronic liver disease). d = day.

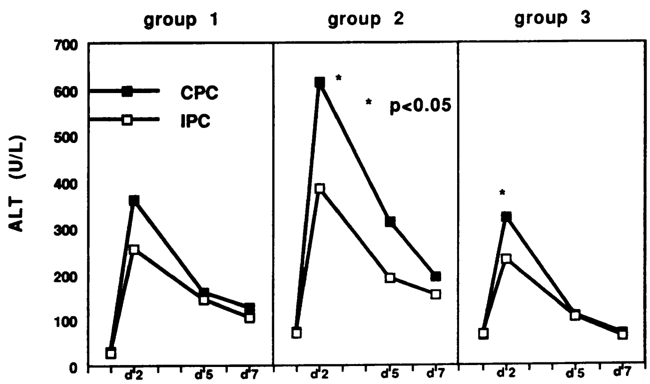

Figure 3. Serial changes in serum alanine aminotransferase of patients after hepatic resection with CPC and IPC, according to the nature of underlying liver parenchyma: group 1, patients with normal liver; group 2, patients with steatosis ≥20%; and group 3, patients with chronic liver disease). d = day.

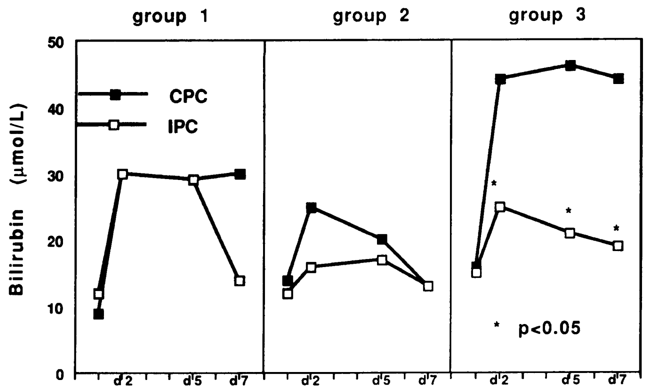

Figure 4. Serial changes in serum total bilirubin of patients after hepatic resection with CPC and IPC, according to the nature of underlying liver parenchyma: group 1, patients with normal liver; group 2, patients with steatosis ≥20%; and group 3, patients with chronic liver disease). d = day.

although there was significantly more bleeding in the IPC group during parenchymal transsection, there was no statistical difference in the total operative blood loss between the two groups. The higher blood loss in the IPC group is probably related to bleeding from the vessels of the part to be removed, which were left unsecured and just compressed during the reperfusion period. Securing both sides of the transsection margin would have increased the ischemic period in the IPC group.

Overall, two thirds of the patients did not require any blood transfusion, and it is likely that this figure, comparable to that reported by other specialized centers, will improve in the future.[26-28] Our data suggest decreased bleeding during liver resection will not necessarily be achieved by improved clamping techniques. Vascular occlusion is of no help in limiting blood loss during the period of dissection and mobilization of the liver, which accounted for 60% of the overall blood loss in the present study. Bleeding at this initial stage is mainly related to the size of the lesions, their hypervascularization, local extension, previous adhesions, and portal hypertension, particularly when these tumors involve the right liver.[29]

Intermittent clamping has a very important albeit unquantifiable advantage over CPC in that it allows surgeons to perform the hepatectomy without haste. The periods of unclamping in particular can be used by the operating team to relax and assess the tumor-free margins using intraoperative ultrasound. The ability to increase the overall duration of clamping safely also allows large and difficult hepatectomies to be performed.[30] In this setting, if significant backflow bleeding occurs, IPC should be combined with extraparenchymal control of the hepatic veins, because the caval flow cannot be interrupted and released sequentially.[16]

In conclusion, although the amount of blood loss is increased during liver transsection under IPC, the current study provides evidence of the superiority of IPC over CPC in terms of parenchymal tolerance to ischemia, especially in the presence of a preexisting liver disease. IPC also allows an increase in the ischemia time and hence allows the performance of difficult hepatectomies that would otherwise be considered impossible for tumors arising in livers with abnormal parenchyma.

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